determining the ~~interaction between~~ the agent and the nucleic acid molecule or the ~~expression~~ product as a determination of the disorder.

## Remarks

Applicants have amended claim 1 to clarify claim language. No new matter has been added. Pursuant to a telephone conversation with the Examiner on June 5, 2001, Applicants affirm the election of NA group 1 nucleic acid molecules for prosecution.

## Rejections Under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 1, 2, and 117-127 under 35 U.S.C. 112, first paragraph, as lacking adequate written description. The Examiner asserted that an adequate written description of NA group 1 nucleic acid molecule fragments "requires more than a mere statement that it is part of the invention and reference to potential fragments containing unspecified molecular structures/sequences of molecules that are essential for the making the genus fragments of NA group 1 nucleic acids molecules as claimed." Applicants respectfully traverse the rejection.

The controlling case law for an adequate written description of a nucleic acid molecule is *University of California v. Eli Lilly and Co.* and cases cited therein. *University of California v. Eli Lilly and Co.* 43 USPQ 2d 1398 (Fed. Cir. 1997). In the *Lilly* case, the Court held that a generic statement referring to a nucleic acid molecule such as "vertebrate insulin cDNA" was not an adequate written description of the nucleic acid molecule because it did not distinguish the claimed molecule from others in the genus of like molecules except by its functional aspects. *Id.* at 1406. The problem with the written description of an insulin cDNA in the University of California application was that it "does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." *Id.* The Court further stated that a proper written description "of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to

the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under §112, paragraph 1, by showing the enablement of a representative number of species within the genus." *Id.*

Therefore, the Court in *Lilly* decided that a description of a genus of nucleic acid molecules which was only functional was not an adequate written description of that set of nucleic acid molecules. That problem is plainly not shared by the disclosure of Applicants in the instant application. The question which must be asked is whether there is an adequate written description of a nucleic acid molecule under the present case law, which "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Id.* at 1404, citing *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

Applicants have provided both structural and physical properties of the claimed nucleic acid molecules, and therefore Applicants assert that they have provided an adequate written description which would allow one skilled in the art to "visualize or recognize the identity of the members of the genus." *Lilly*, 43 USPQ 2d at 1406.

The NA group 1 nucleic acid molecule fragments as claimed are set forth in detail in the specification. At page 19, lines 23-24, Applicants define a unique fragment as "one that is a 'signature' of the larger nucleic acid", the larger nucleic acid selected from the group consisting of SOX2 (SEQ ID NO:3), SOX1 (SEQ ID NO:4), ZIC2 (SEQ ID NO:5), SOX3 (SEQ ID NO:11) and SOX21 (SEQ ID NO:12). The aforementioned NA group 1 nucleic acid molecules have specified nucleic acid sequences set forth in the application. Accordingly, fragments of NA group 1 nucleic acid molecules would also have specific molecular structures and sequences and would not be "unspecified molecular structures/sequences". The passage from page 19, line 24 - page 21, line 1 provides further descriptions of NA group 1 nucleic acid molecule fragments. The passage states that unique fragments are typically between 12 and 32 nucleotides and exclude fragments completely composed of the nucleotide sequences of any of GenBank accession numbers listed in Table 4 of the specification/application or other previously published sequences as of the filing date of the priority documents for sequences listed in a respective priority document or the filing date of this application for sequences listed for the first time in this application which overlap the sequences of the invention. Accordingly, Applicants believe that the specific attributes of NA group 1 nucleic acid molecule fragments were set forth in the specification.

In *Lilly*, the Court stated that the recitation must be "of a representative number" of nucleic acids, and then analogized this requirement to the enablement of a representative number of species within a given genus. *Id.* at 1406. In this regard, the Court cited with favor the case of *In re Grimme*, 274 F.2d 949, 952 (CCPA 1960): "It may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'" *Id.* In the specification, Applicants have described specifically the structures of SEQ ID Nos:3, 4, 5, 11, and 12, as well as nucleic acids which hybridize under stringent conditions to those sequences. Applicants maintain, therefore, that the disclosure contained in the specification is sufficient to identify a representative number of species of the claimed genus of nucleic acids. There is no requirement under the law that the sequences claimed must be individually disclosed in the specification. As was made clear by the Court in *Lilly*, a genus is "fully described" when one can "visualize or recognize the identity of the members of the genus" by sequence or other structural features (in this case, stringent hybridization to known sequences), physical properties (e.g. expression results disclosed in Examples) etc.

Enablement

The Examiner also rejected claims 1, 2, and 117-127 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of NA group 1 nucleic acid molecules that hybridize to NA Group 1 nucleic acid molecules in a biological sample from a subject, does not reasonably provide enablement for any and all fragments thereof that hybridize to NA Group 1 nucleic acid molecules.

Applicants respectfully traverse this rejection. Assuming for the moment that the Examiner has met the burden of providing reasons for doubting the assertions made by Applicants, and taking into consideration the Examiner's statements with respect to undue experimentation, Applicants still maintain that the claimed invention is enabled. Determination of enablement of a claimed invention follows from the analysis of the eight *Wands* factors. *In re Wands* 858 F.2d 731, 737, 740, 8 U.S.P.Q.2d 1400, 1404, 1407 (Fed. Cir. 1988). It appears that only some of these factors were considered by the Examiner; however, all of the factors should be considered for a proper analysis.

The factors to be considered in determining whether a disclosure would require undue experimentation include: 1) predictability of the art, 2) the amount of direction or guidance

presented, 3) the presence or absence of working examples, 4) breadth of the claims, 5) the nature of the invention, 6) quantity of experimentation, 7) the state of the prior art, and 8) the level of one of ordinary skill in the art. Applicants maintain that full consideration of each and all of the *Wands* factors, in view of the state of the art at the time of filing, leads one to the reasonable conclusion that practicing the invention would not require undue experimentation.

The Examiner has asserted that in view of the unpredictability of the art of cancer antigen precursors, the limited guidance provided in the specification, the limited scope of working examples, and the "lack of enabling data", it would have required one of skill in the art at the time of filing undue experimentation to make and/or use the claimed invention. Applicants respectfully disagree with the Examiner's assertions, as follows.

Predictability of the art:

The Examiner asserts that the art surrounding cancer antigens is still developing, and is, therefore, still unpredictable. The fact that the art surrounding a particular field is still developing does not render it unpredictable. As a matter of fact, the arts surrounding most of the scientific and biomedical fields are still developing yet many, including the art of nucleic acid hybridization, are predictable. In the instant application, the claims include nucleic acid fragments. One of ordinary skill in the art certainly would know of several ways to make and use fragments of nucleic acids. Moreover, the person of ordinary skill knows that one cannot use a single nucleotide "fragment" in hybridization. Nucleic acid hybridization has been known and practiced for many years such that the preparation and use of nucleic acid molecules in hybridization is a basic skill of even inexperienced molecular biologists. One of ordinary skill in the art of molecular biology, protein chemistry and immunology can reliably predict, make and use the nucleic acid fragments as claimed in the application.

The Examiner also states that merely because nucleic acid molecules hybridize to the sequences in cancer cells, or cells associated with a disorder that is characterized by the expression of these antigens, does not mean that it will function as a reliable method of diagnosis for cancer or other disorders. Respectfully, this assertion has nothing to do with the "predictability of the art" factor. Applicants maintain that the predictability of determining the expression of nucleic acid molecules and expression products thereof is high. Given the nucleic acid molecules disclosed in the specification, one of ordinary skill in the art can predictably

examples together with the ample technical details in the specification and the knowledge of one of ordinary skill in the art at the time of filing of the application provide enough guidance to one of ordinary skill in the art at the time of filing to make and use the claimed invention. Thus alleged lack of working examples is not a sufficient reason to support a finding of undue experimentation.

With respect to working examples, the court in *In re Wright* stated that "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright* at 1561 *citing In re Marzocchi* 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971). Applicants have provided not only broad terminology which is readily understandable to one of ordinary skill in the art, but also illustrative examples as noted above.

It does not appear that the Examiner considered the remaining *Wands* factors: 1) breadth of the claims, 2) the nature of the invention, 3) quantity of experimentation, 4) the state of the prior art, and 5) the level of one of ordinary skill in the art. Applicants submit that none of these factors would weigh against a finding of enablement for the claimed invention. For example, very little experimentation is required to make, test and use the claimed nucleic acids encoding NA group 1 nucleic acid molecules once the sequences of those molecules are provided, as was done in the instant application. Given the advanced state of the art, one of ordinary skill in the art would only require routine experimentation to test the claimed nucleic acids. Accordingly, any experimentation required would not be undue.

The last two *Wands* factors are crucial to any determination of undue experimentation. In the *Wands* case, for example, the court's decision turned on the "high level of skill in the art at the time the application was filed", and that "all of the methods needed to practice the invention were known." *Wands* at 740, 8 USPQ2d at 1406. Applicants maintain that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, and therefore must weigh heavily in favor of a finding that undue experimentation is not required.

The level of skill in the art has an important effect on the amount of guidance which must be provided to enable the invention. As the court stated in *In re Howarth*, "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*,

654 F.2d 103, 105 (C.C.P.A. 1981). Thus the level of knowledge of one of ordinary skill in the art cannot be ignored in the *Wands* factor analysis. For the standard nucleic acid diagnostic procedures claimed in the application, the level of skill in the art is high. Applicants maintain that the person of skill in the art would know how to prepare, test and use the claimed nucleic acids. Accordingly, Applicants assert that the claims are enabled throughout their scope.

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the rejection of the claims under 35 U.S.C. §112, first paragraph.

**Rejections Under 35 U.S.C. §112, Second Paragraph**

The Examiner rejected claims 1, 2 and 117-127 under 35 U.S.C. 112, second paragraph as being indefinite. Applicants have amended claim 1 to clarify the claim language. Accordingly, Applicants respectfully request reconsideration of the claim as amended and withdrawal of the rejection under 35 U.S.C. 112, second paragraph.

Applicants respectfully request reconsideration of the claims in view of the amendments and reasoned statements made above. If the Examiner wishes to advance the prosecution in any way, or if the amendment is defective or unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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Dated: October 22, 2001
**X10/21/01**

**Amended Claims:**

1. (amended) A method of diagnosing a disorder characterized by expression of a human cancer associated antigen precursor coded for by a nucleic acid molecule, comprising:

contacting a biological sample isolated from a subject with an agent that [specifically] binds under stringent hybridization conditions to the nucleic acid molecule, an expression product thereof, or a fragment of an expression product thereof complexed with an HLA molecule, wherein the nucleic acid molecule is a NA Group 1 nucleic acid molecule, and

determining the interaction between the agent and the nucleic acid molecule or the expression product as a determination of the disorder.